to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat, wherein said nucleotide numbering is based upon HIV-1 strain NL4-3.

REMARKS

In the Final Action dated September 26, 2001, claims 49-50, 66-67, 85 and 120-136 are pending and are under consideration. Claims 49-50, 66-67, 85 and 120-136 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support. Claim 85 is rejected under 35 U.S.C. §112, second paragraph as allegedly referring to features of non-elected subject matter. Claims 122, 124, 129 and 134 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

This Response addresses each of the Examiner's rejections. Applicants therefore respectfully submit that the present application is in condition for allowance or at least better condition for appeal. Favorable consideration of all pending claims is therefore respectfully requested.

Claims 49-50, 66-67, 85 and 120-136 are rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enabling support.

Claims 49-50, 66-67 and 120-126 are drawn to methods for vaccinating an individual against the development of AIDS or AIDS-related diseases by administering to the individual a non-pathogenic isolate of HIV-1. Claims 85 and 127-136 are drawn to therapeutic compositions useful for inhibiting or reducing productive infection by a pathogenic strain of HIV, which compositions contain a non-pathogenic isolate of HIV-1. The non-pathogenic isolate of HIV-1 recited in the instant claims is further characterized as comprising a deletion in the region

corresponding to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat (which region comprises the nucleotide sequence coding for amino acids 166-206 of the *nef* protein).

The Examiner contends that the specification fails to provide adequate guidance concerning the selection of allelic variants of *nef* or any other HIV viral gene that would be non-pathogenic. The Examiner points out that the SBBC patients described in the specification were all infected with the same parental virus having a deletion in the *nef*/LTR region. The Examiner contends that it is not clear whether the non-pathogenicity feature associated with the HIV isolates obtained from these SBBC patients can be extended to other HIV-1 isolates, particularly in view of the teaching by Terwilliger et al. (1991). Terwilliger et al. reported that within the same genetic context, the IIIB *nef* allele slightly retards replication of the virus in a T-cell line, whereas the ELI *nef* allele accelerates replication of the virus.

Applicants respectfully submit that the claimed methods and compositions do not involve the use of just any variant (i.e., all variants) of the *nef* gene. Rather, the non-pathogenic isolate of HIV-1 recited in the instant claims is characterized as comprising a deletion in the region corresponding to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat (which region comprises the nucleotide sequence coding for amino acids 166-206 of the *nef* protein).

While Applicants recognize that other mechanisms (including other types of alterations in the *nef* gene or LTR) may influence the pathogenicity of HIV-1, deletion in the particular region of the *nef* gene or LTR as recited in the claims clearly result in the non-pathogenicity of the exemplified strains which can then be used as vaccines against pathogenic HIV strains.

The Examiner also contends that the specification fails to demonstrate that the instantly claimed HIV-1 vaccines or therapeutics employing *nef* deletion variants would mount an efficacious humoral or cellular immune response resulting in the *prevention or treatment* of HIV infection. The Examiner has pointed out a number of problems associated with vaccine development, evidenced by various reports published in the field.

In this regard, Applicants previously submitted an article published by Dyer et al. (*J. Virol. 73*: 436-443, 1999, as Exhibit C in the Amendment filed on June 19, 2001), which reported the effectiveness of the Sydney Blood Bank Cohort (SBBC) strain of HIV-1 as an immunogen. In the study conducted by Dyer et al., the donor (D36) and the six recipients were studied for HIV-1 specific cytotoxic T-cell activity by four techniques. Four (D36, C18, C49, C98) of the seven had strong anti-HIV-1 cytotoxic T-cell responses, and one (C135) had no detectable response. It is also known (although not reported in this paper) that all SBBC members, except C135, had strong antibody responses.

The Examiner points out that Dyer et al. was published after the filing of the present application. The Examiner states that publications dated after the filing date generally cannot be used to show what was known at the time of filing. Thus, it is the Examiner's opinion that this exhibit cannot be properly relied upon to demonstrate that the instant application was enabled at the time of filing.

It is respectfully submitted that Dyer et al. was submitted in response to the Examiner's concern that Applicants have not shown whether any of the non-pathogenic HIV isolates is able to invoke an immune response. Dyer et al. demonstrate that the majority of the non-pathogenic HIV isolates disclosed in the present application did provoke a CTL response. That is, the reference was provided as evidence of what is asserted to be the immunogenic

capacity (i.e., an inherent property) of the non-pathogenic HIV isolates of the present application. It is respectfully submitted that the weight of such evidence should not be affected by the fact that it was first disclosed after the filing of the instant application. It is further respectfully submitted that all the techniques used by Dyer et al. in determining HIV-1 specific CTL responses in a SBBC donor, including enzyme linked immunoblot, tetrameric complex binding, direct CTL lysis, and CTL precursor level techniques, were available to those skilled in the art at the time the present application was filed.

As further support of the efficacy of the non-pathogenic HIV isolates employed in the presently claimed methods and composition, Applicants provide herewith an article by Kent et al. (attached hereto as **Exhibit A**), entitled "*Vaccination with attenuated simian immunodeficiency virus by DNA inoculation*", published in *Journal of Virology* 75:11930-19934, 2001.

In essence, the Kent et al. article describes the delivery of attenuated lentivirus vaccine as pro-viral DNA. A molecular clone of SIV_{mac239} (analogous to $HIV\text{-}1_{nl43}$ referred to in the present application) was used. A deletion was made to SIV_{mac239} in the 3'-LTR region, which is equivalent to the deletion of nucleotides 9281-9348 of $HIV\text{-}1_{nl43}$ in the *nef*/LTR region described in the present specification. A second construct was also made which contained, in addition to the deletion in the 3' LTR region, a deletion in the 5' LTR region.

Pig-tailed macaques (*Macaca nemistrina*) were inoculated with the SIV construct DNA as follows: four received wild-type SIV_{mac239} and two each received the two different SIV deletion constructs. Macaques receiving the wild-type SIV developed and retained high viral loads (greater than 1 million copies/ml plasma), had a marked decline in $CD4^+$ cells. It took

fewer (only 10,000) monkey peripheral blood mononuclear cells (PBMC) to isolate virus, which evidences a larger number of infected PBMC.

Monkeys receiving the deletion constructs had initial peak in viral loads of a maximum of 1 million copies/ml plasma, which then decreased to below detectable levels (i.e. 1500 copies/ml). One of the monkeys (designated M16 and inoculated with the deletion construct comprising the single 3'-LTR deletion) later had an increase in viral load and a decline in $CD4^+$ count to less than 70% of pre-inoculation levels. It was subsequently determined that the construct comprising the single 3'-LTR deletion in M16 was able to recombine with wild-type 5'-LTR sequence to repair the deletion, which resulted in a loss of attenuation and a progression to disease.

Three remaining monkeys inoculated with the deletion SIV constructs were challenged with the wild type SIV_{mac239} virus. Three naïve control monkeys became infected, had peak SIV viral loads, maintained viral loads of greater than 1 million copies/ml and had declining $CD4^+$ counts, as expected. All three vaccinated monkeys were protected from a high peak level of SIV viral load as seen in the control monkeys. Two of the monkeys vaccinated with the deletion constructs maintained low viral loads and normal $CD4^+$ levels throughout a 30-week follow up period. These two had high levels of IFN-γ production (T cell immunity) in response to SIV antigens both before and after challenge.

In summary, SIV constructs mimicking the HIV-1 constructs disclosed in the present application having a deletion in the *nef*/LTR region protected monkeys from challenge from virus infections. Consequently, Applicants respectfully submit that the Kent et al. article provides evidence of the effectiveness of the non-pathogenic HIV-1 isolates employed in the presently claimed methodology and compositions. It is important to recognize that there is no

evidence that a wild-type HIV strain exists in the cohort members who all received a transfusion from a common donor, as disclosed in the present application, provides further evidence that the attenuated strains to which they were exposed likely have induced some protective effect against exposure to wild-type virus.

Clearly, it would be unrealistic and it is not required under the law to obtain actual clinical data using the attenuated viruses disclosed in the present application in order to satisfy the enablement requirement.

In view of the foregoing, Applicants respectfully submit that the rejection of claims 49-50, 66-67, 85 and 120-136 under 35 U.S.C. §112, first paragraph, is overcome. Withdrawal of the rejection is therefore respectfully requested.

As further set forth in the Final Action, claim 85 is rejected under 35 U.S.C. §112, second paragraph as allegedly referring to features of non-elected subject matter.

Claim 85 presently recites "a therapeutic composition useful for inhibiting or reducing productive infection by a pathogenic strain of HIV-1 and/or for vaccinating an individual against the development of AIDS or AIDS-related diseases." The Examiner indicates that the claim should be amended to reflect the election, e.g., to recite "a vaccine composition comprising a non-pathogenic HIV-1 isolate."

It appears to Applicants that by "non-elected subject matter", the Examiner is referring to the language in the preamble "useful for inhibiting or reducing productive infection by a pathogenic strain of HIV-1". Without acquiescing to the Examiner's contention, Applicants have amended claim 85 as the Examiner has suggested in an effort to expedite the prosecution of the present application. As such, the rejection of claim 85 under 35 U.S.C. §112, second paragraph, is overcome. Withdrawal of the rejection is respectfully requested.

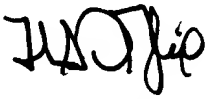
Claims 122, 124, 129 and 134 are rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite. The claims include the recitation "about 10 nucleotides". The Examiner contends that it is not clear whether such recitation would encompass a deletion of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, or 15 nucleotides.

Applicants respectfully submitted that the use of the term "about" in claims is well accepted under the law (see, e.g., Syntax Inc. v. Paragon Optical, Inc., 7 U.S.P.Q. 2d 1001 (D. Ariz. 1987), and is clearly understood by those skilled in the art. However, in order to favorable advance the prosecution of the present case, Applicants have deleted the term "about" from the rejected claims without prejudice. Accordingly, withdrawal of the rejection of claims 122, 124, 129 and 134 are rejected under 35 U.S.C. §112, second paragraph, is respectfully requested.

Attached hereto is a marked-up version of the changes made to the claims by the instant amendment, captioned "**Version with Markings to Show Changes Made.**"

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



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Encls.: Version with Markings to Show Changes Made; Exhibit A.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Please amend the claims as follows:

85. (Twice Amended) A [therapeutic] vaccine composition [useful for inhibiting or reducing productive infection by a pathogenic strain of HIV-1 and/or for vaccinating an individual against the development of AIDS or AIDS-related diseases, said composition] comprising a non-pathogenic isolate of HIV-1 and at least one of a pharmaceutical acceptable carrier or a diluent, wherein said isolate comprises a genomic deletion in the region corresponding to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat, wherein said nucleotide numbering is based upon HIV-1 strain NL4-3 and said region comprises the nucleotide sequence coding for amino acids 166-206 of the *nef* protein.

122. (Amended) The method of claim 49, wherein said deletion comprises at least [about] 10 nucleotides.

124. (Amended) A method for vaccinating an individual against the development of AIDS or AIDS related diseases, said method comprising administering to said individual a non-pathogenic isolate of HIV-1 in an amount effective to infect target cells and to generate target cells carrying DNA derived from said non-pathogenic isolate of HIV-1, wherein said isolate comprises a genomic deletion of at least [about] 10 nucleotides in the region corresponding to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat, wherein said nucleotide numbering is based upon HIV-1 strain NL4-3.

129. (Amended) The therapeutic composition of claim 85, wherein said deletion comprises at least [about] 10 nucleotides.

134. (Amended) A therapeutic composition useful for inhibiting or reducing productive infection by a pathogenic strain of HIV-1 and/or for vaccinating an individual against the development of AIDS or AIDS-related diseases, said composition comprising a non-pathogenic isolate of HIV-1 and at least one of a pharmaceutical acceptable carrier or a diluent, wherein said HIV-1 strain comprises a genomic deletion of at least [about] 10 nucleotides in the region corresponding to nucleotides 9281-9438 of the *nef* gene and U3 long terminal repeat, wherein said nucleotide numbering is based upon HIV-1 strain NL4-3.